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EXAMINER	
NGUYEN, DAVE TRONG	

ART UNIT	PAPER NUMBER
1632	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/234,606	Wolff
Examiner	**Art Unit**
Dave Nguyen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1 and 18-48* is/are pending in the application.

4a) Of the above, claim(s) *18 and 19* is/are withdrawn from consideration.

5) ☒ Claim(s) *43-45* is/are allowed.

6) ☒ Claim(s) *1, 20-42, and 46-48* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Jan 21, 1999* is/are a) ☐ accepted or b) ☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Claims 3-17 have been canceled, claims 20-48 have been added by the amendment filed April 14, 2003.

Claims 18-19 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention. A complete response to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) MPEP 821.01.

Claims 1, and 20-48, to which the following grounds are applicable, are pending.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, and 20-42, 46-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite in the recitation of "a complex consisting of a polynucleotide and a chelator" and yet the claim further claims that "one or more components of the complex" interacts with the chelator, *e.g.,* see claim 1, for example. Clarification is request. Along the same reasoning, it is not apparent how a complex consisting of just a polynucleotide and a chelator can at the same time contains other components such as a cell receptor signal, a releasing signal, a steric stabilizer or a hydrophobic group covalently linked to the chelator, *e.g.,* see claims 26, 38.

The examiner suggests to applicants that in order to obviate the above rejection and at the same reduce potential prior art issues, the claims should be amended as follows:

1. A process for delivering a polynucleotide to a cell comprising:

a) forming a complex consisting of a chelator and a nucleic acid vector which comprises a polynucleotide and at least one or more components, wherein an electrostatic interaction of the chelator with said one or more components of the nucleic acid vector requires the presence of a metal ion coordinated by the chelator.

b) delivering the complex to the cell.

Cancel claim 38 or amending claim 38 as being dependent from claim 39, and the amended claim can be rewritten as follows:

38. The process of claim 39, wherein the primary amine-containing molecule is covalently linked to the chelator.

Should an amendment after final proposes claims that are different and distinct from that of the proposed claims, the amendment may not be entered due to potentially prior art issues and new considerations.

To the extent that the claims 1, and 20-48 embrace:

A process for delivering a polynucleotide to a cell comprising:

a) forming a complex consisting of a chelator, which chelator is covalently linked to a polyamine and is bound or coordinated by a metal ion (being used as a contrast agent), which metal bound chelator/polyamine/ligand is electrostatically complexed to nucleic acid vector which comprises a polynucleotide and at least one or more components (targeting ligands, stabilizers), wherein an electrostatic interaction of the chelator with said one or more components of the nucleic acid vector requires the presence of a metal ion coordinated by the chelator.

b) delivering the complex to the cell

The following ground rejection remain applicable:

Claims 1, 20, 22-30, 32-42 are rejected under 35 U.S.C. 102(b) as being anticipated by, or in the alternative, under 35 USC 103(a) as being unpatentable over Kayyem *et al.*, (WO 96/11712, IDS).

Kayyem teaches a process for delivery an anionic polymer (DNA/targeting ligand) which is electrostatically complexed to cationic polymer complex conjugated to a plurality of chelators bound to a metal ion+ (page 8, first and second paragraphs; page 9, second paragraph, page 10, third paragraph, page 11, second paragraph, pages 12 and 13, and pages 26-32. Kayyem teaches that a plurality of

chelators can be added to the -NH2 groups of the lysine side chains as linkers for binding to a plurality of contrast agents (page 10, third paragraph), and that a chelator can be conjugated to any of the disclosed polymeric molecule (page 12). Cell targeting moieties and physiological agents including therapeutic agents, are attached to one or both of the polymeric molecules (abstract). Furthermore, the abstract clearly states:

> The delivery vehicles can be used in clinical protocols in which nucleic acids for gene therapy [expressible nucleic acids] and agents for MRI contrast are co-transported to specific cells allowing medical imaging monitoring of nucleic acid delivery.
>
> (Also see page 4, lines 16-22).

On page 5, Kayyem states that "In another embodiment, one of the polymeric molecules comprises a nucleic acid which is complexed [electrostatically] with one or more polymeric molecules comprising a polyamine.

With respect to the limitation of recharging the polychelator to change the net charge and the limitation of an expressible nucleic acid being a first polyanionic polymer or molecule, Kayyem teaches the same on pages 7 and 8. More specifically, Kayyem states:

> The delivery of the present invention comprise a fist polymeric molecule [expressible nucleic acid] and a second polymeric molecule [polycationic molecule, a complex composed of polylysine and a chelator, see page 10]. As indicated in Figure 1A, the delivery vehicle (1) comprises a first polymeric molecule (2) having an overall net positive or negative charge which is employed as a scaffold to which an oppositely charged second polymeric molecule (3) is complexed. As shown in Figure 1B, some delivery vehicles include a third polymeric molecule (6) having a net charge opposite that of the first polymeric molecule and complexed with the first polymeric molecule. Preferably the first and second polymeric molecules are held together by electrostatic interactions and thus do not need to be covalently linked to each other. In certain embodiments, both the first and second polymeric molecules contain a mixture of charged groups and thus are zwitterionic.

The depiction of linear polymeric molecules in Figure 1 is for illustrative purposes and is not necessarily preferred, as circular polymers such as plasmids [expressible nucleic acids] may also be used. The delivery vehicle will be in any configuration that is suitable for cellular uptake. (page 7);

In a preferred embodiment, the nucleic acid is double stranded, most preferably a double stranded plasmid (page 8).

Thus, Kayyem does teach that the second polymeric molecule can be recharged by preparing the molecule so as to contain a mixture of charged groups and/or by complexing a third polymeric molecule to the nucleic acid polymer.

More specifically as to the expressible plasmid, Kayyem states on page 8:

In one embodiment, the nucleic acid encodes a reporter gene, such that the uptake of the delivery vehicle can be additionally monitored by the presence or absence of the reporter gene and/or the protein encoded by the gene [protein expressed by the nucleic acid].

More specifically as to the use of the delivery vehicle to deliver and express a therapeutic protein encoded nucleic acids for gene delivery and/or gene therapy, Kayyem teaches the same on page 8 through page 9.

More specifically as to the second polymeric molecule being a modified polysine composed of lysine/chelator based monomers linked by a covalent bond, Kayyem teaches on page 10:

When polylysine is used as the second polymeric molecule, the –NH2 group of the lysine side chains at high pH serve as strong nucleophiles for multiple attachment of activated chelating agents. The invention takes advantage of both the polycationic and polynucleophilic nature of polyamines such as polysine. At high pH the lysine monomers are coupled to the physiological agents under conditions that yield on average 5-20% monomer substitutions. At physiological pH to low pH, the remaining unlabeled positively charged lysines facilitate nucleic acid bindings.

As to the linkage of cell targeting agents and/or physiological agents, Kayyem states on page 11:

The cell targeting moieties and physiological agents described below are attracted to either polymeric molecule, although in a preferred embodiment they are both attached to the polycation.

In addition and to particularly point out that the invention is not directed *per se* to just the delivery of contrast agents such as paramagnetic or superparamagnetic metals, Kayyem states clearly on the first paragraph of page 12:

By the term "physiological agent" herein is meant compounds which are desirable to deliver in a cell-specific manner. Included in this definition of physiological agents are both contrast agents and therapeutic agents.

Kayyem also recognizes the toxicity of the use of some paramagnetic or superparamagnetic metals as contrast agents, and further provide a solution to the problem by teaching on page 12:

Gd(III) ions are extremely toxic to cells and therefore must be bound to a chelating agent which is ten conjugated to the polymeric molecule [second polymeric molecule, for example]. A number of chelating agents is further taught by Kayyem as being disclosed in a number of US patents as cited on page 12 of Kayyem.

In addition, Kayyem discloses on page 26 that pharmaceutically acceptable carriers including a salt are employed in the preparation of a conjugate of chelators and a cationic polymer.

Absent evidence to the contrary, the delivery process and the compositions or conjugates disclosed in Kayyem have all of the properties cited in the claims, and to the extent that any minor modification such that types of bonding and/or an incorporation of more charges so as positive charges are abundant to enhance the delivery of nucleic acid into target cells, it would have been obvious for one of ordinary skill in the art have modified such changes so long as such modifications are within the teaching of the Kayyem reference so as provide addictive effects in enhancing the delivery of the nucleic acid into a target cell for expression.

Applicant's response (page 5) has been considered by the examiner but is not found persuasive

because of the reasons as set forth in the stated rejection. More specifically, the issue is that applicant assert that Kayyem does not teach that a metal ion is bound or coordinated by a chelator, and that the function of the metal bound chelator in enhancing a non-covalent, reversible interaction of components of a nucleic acid complex as claimed. However, given that there exists a non-covalent, reversible interaction between the nucleic acid polymer complex and the cationic polymer complex conjugated to a plurality of chelators bound to a metal ion+, and that the chelator is bound by or coordinating the metal ion used as a contrast agent, it would necessarily flow from the teaching of Kayyem that the metal bound chelator enhances a non-covalent, reversible interaction of components of a nucleic acid complex and the cationic polymer complex as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, and 20-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kayyem *et al.* taken with Hnatowich *et al.* (US Pat No. 5,980,861).

To the extent that Kayyem does not teach explicitly crown ether or polymers associated with a plurality of crown ether chelators, Hnatowich teaches that it is routine in the art at the time the invention was

made for one of ordinary skill in the art to employ known chelators including crown ether for conjugation to a polymer either by covalent bonding or ionic bonding for purpose of real time monitoring of the delivery of polymers including DNA (entire document, especially columns 11 and 12). More specifically, Hnatowich *et al.* teach on column 2 bridging column 3; column 3 bridging column 4; column 6, last paragraph; column 9, first paragraph; column 11, lines 1 to lines 54; column 12 bridging column 13; column 19, first paragraph; and columns 43 and 44:

A process for delivery of radiolabeled nucleic acid molecules or radiolabeled peptide nucleic acid to a cell, which process comprises associating a crown ether to either a nucleic acid polymer or a peptide nucleic acid polymer through a polyamine linker (which is positive charged within its own biochemical structure), mixing the crown ether containing nucleic acid polymer with a polymer carrier, and delivering the crown ether containing nucleic acid polymer complexed with the polymeric polymer to a cell. As the result of the teaching provided by the Hnatowich *et al.* reference, the crown ether based chelator is electrostatically linked to a cDNA by a positive charged linker, *e.g.,* polyamine. Not only that '861 patent teach complexes of nucleic acid molecules associated with a chelator, the patent on column 19 further teaches that polymeric carriers including polyglycolic acid can be associated or linked to the DNA-chelator complex as controlled release formulation to enhance the delivery of DNA polymer to a target cell.

It would have been obvious for one of ordinary skill in the art to employ any chelator including crown ether bound to polylysine in the conjugate or composition of Kayyem. One of ordinary skill in the art would have been motivated to have employed crown ether as a chelator or polychelator for the purpose of either conjugating covalently to the -NH2 moiety of the cationic polymer such as polylysine because Hnatowich teaches that chelator moieties of crown ether are known in the prior art as effective chelators for use in real time monitoring of the delivery of polymers to cells *in vivo,* and because Kayyem *et al.* teaches that any of the known paramagnetic metal ion chelators attached covalently to the -NH2 moiety of the cationic polymer such as polylysine can be used for the purpose of real time monitoring of the delivery of polymers including expressible to target cells *in vivo* for the purpose of gene delivery and/or gene therapy

set forth in any prior art.

Thus, the claimed invention as a whole was *prima facie* obvious.

Applicant's response (page 6) has been considered by the examiner but is not found persuasive because of the reasons set forth in the above discussion of applicant's response. Furthermore, the fact that Hnatowich does teach an ionic interaction even just for only one time does indicate that at the time the invention was made, the totality of the prior art does teach an ionic interaction between a chelator and a desired polymer such as DNA is known, and that applicant's response does not provide any substantial evidence demonstrating that the prior art teaches away from the claimed invention, and that a reasonable expectation can not be achieved by one of ordinary skill in the art such as those with a high level skill in polymer chemistry, as evidenced the teachings provided by the totality of the prior art of record.

Claims 1, and 20-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kayyem *et al.* taken with Hnatowich *et al.* (US Pat No. 5,980,861), and further in view of Volkin (WO 97/40839).

To the extent that Kayyem taken with Hnatowich does not teach the presence of metallic contaminants in a DNA formulation,

Volkin teaches a DNA vaccine formulation for use in delivering an expression DNA vector encoding a therapeutic antigen to a mammalian cell *in vivo,* wherein the formulation consists essentially of metal contaminants and the vector, wherein an incorporation of a metal chelator such as NTA (nitrilotriacetic acid) and DTPA (diethylenetriaminepentaacetic acid) is employed to detoxify metals, wherein the metal chelator comprises binding sites which function as to bind to metal ions contained in the formulation, wherein such binding results in a coordination between the metal ion and the chelator.

It would haven obvious to one of ordinary skill in the art to have employed any polychelator complex and/or chelator complex as taught in the combined cited references of Kayyem taken with Hnatowich in any DNA formulation containing metallic contaminants. One of ordinary skill in the art would have been motivated to employ any of the polychelator complexes taught in the Kayyem taken with Hnatowich

references because the combined references teach that not only the polychelator complexes are effective to detoxify metallic ions, the complexes can be used to enhance the targeted delivery of any DNA to a cell *in vivo*.

Thus, the claimed invention, as a whole, was *prima facie* obvious.

Claims 43-45 are in condition for allowance.

No claim is allowed.

The drawings are objected because of the PTO-948 attached to the office action dated 2/15/000. **A complete response to this office action must include a response to the objection or a filing of corrected drawings so as to obviate the objection.**

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024.**

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Trong Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER